REMARKS

I. Preliminary Remarks

Applicants wish to thank the Examiner for the courtesy shown the undersigned attorney during the telephonic interview conducted May 14, 2002. During that interview distinctions between Applicant's invention and the disclosures of the prior art were discussed and the Examiner reported that she believed that the claims were free of the art for the reasons expressed below. The compositions of the buffer reagents were also discussed as was the question of whether the buffer was critical to the demonstration of unexpected results evidenced in the data presented in the tables on pages 8 and 9 of the application. Applicant confirms in the accompanying Declaration, (which has been approved by the Inventor and a signed version of which will presently be submitted to complete the file) that the buffer recited in claim 2 is not critical to the demonstration of the unexpected results presented on pages 8 and 9 of the application. The specification at page 7, lines 2 and 3 describes a commercially available nucleotide buffer (N5000/N5500 Amersham International plc) which comprises Tris-HCl, ph 7.8, $MgCl_2$ and 2-mercaptoethanol. The specification further teaches that other buffers could be used depending upon the particular polymerase enzymes used as would be clear to those of ordinary skill in the art. (See page 4, lines 13-17).

Finally, claim 1 has been amended to incorporate the elements of claim 2 reciting reagents of the composition and claim 2 has been cancelled as suggested by the Examiner. No new matter is incorporated therein and allowance of remaining claims 1 and 3-6 is solicited.

II. The Outstanding Rejections.

Claims 1-5 stand rejected 5 stand rejected under 35 U.S.C. §103(a) over Suganuma in view of Shen.

Claim 6 stands rejected under 35 U.S.C. §103(a) over Suganuma in view of Shen in view of Hoeltke.

III. The rejections under 35 U.S.C. § 103 should be withdrawn.

The invention relates to an improvement in random priming methods where random sequence oligonucleotides are used to prime DNA synthesis on denatured template DNA at numerous sites along its length. The primer-template complex serves as a substrate

for the "Klenow" fragment of DNA polymerase I and radioactive nucleotides are provided such that newly synthesized DNA is made radioactive. Various kits (See Stratagene) containing solutions of oligonucleotides are known for practice of random priming methods.

There had been a trend toward using longer primers in solution in order to provide more rapid priming. (Megaprime and Ready-To-Go kits) Moreover, Suganuma suggested that shorter primers might be desired for liquid primer solutions because of self-annealing properties of larger primers in solution. Dried primer kits were also known for use with 9-mer and higher primers. (Rediprime, EP 298,269 discloses 15-mers and 17-mers) These were not thought to be subject to the problem of Suganuma. Moreover, there still remained a bias preferring longer primers because of the belief that such longer primers would provide more rapid priming than shorter primers.

The present invention relates to the discovery that there is a self-annealing problem with dried primers and that the solution to that problem is the use of shorter dried primers. Accordingly, the invention is thus directed to dried mixtures of random primers and relates to the discovery that self-annealing occurs when random 9-mers are used in dried predispensed labeling kits. The problem is specific to 9-mers (and longer oligonucleotides) used in dried kits and does not represent a problem with shorter dried primers.

The Obviousness rejections under 35 U.S.C. §103(a) should be withdrawn because (1) the selection of 6-mers to 8-mers does constitutes a critical range (see the application examples) and (2) the art fails to suggest that short primers (6-8 mers) would be desirable in a dried primer system. Thus, Applicant's examples demonstrate a critical difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers.

While Suganuma suggests that the use of 9-mers or longer reduces the priming efficiency of the random primer reaction because of self-annealing of solution-phase primers, the prior art generally taught that longer primers were generally preferred because longer primers have higher melting temperatures (are more specific).

Even if it is accepted that Suganuma suggests the use of shorter primers in kits comprising primers in solution (and it does not) there is no reason to believe that shorter primers would be advantageous in freeze-dried kits in which the primers are inherently more stable. Suganuma fails to make any disclosure regarding dried reagents and Shen, which discloses 48-mer and 22-mer primers (Example 1 and SEQ ID NOS 1 AND 2), fails to

suggest that dried primers should be shortened or any reason why the primers of Suganuma should be dried much less why dried 6-8 mers would be superior to dried 9-mers.

For these reasons, the rejections under 35 U.S.C. §103 (a) should properly be withdrawn and each of claims 1 and 3-6 should be allowed.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. Should the Examiner wish to communicate further with the undersigned attorney on any issue of form or substance she is encouraged to contact the undersigned attorney at the number listed below.

Dated: October 1, 2002

Respectfully submitted,

By _____
Jeffrey S. Sharp
Registration No.: 31,879
MARSHALL, GERSTEIN & BORUN
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorneys for Applicant

Application No.: 09/485245 Docket No.: 28911/36128/US

Version With Markings to Show Changes Made

1. [AMENDED] A labeling composition comprising a random mixture of oligonucleotides which are 6-mers to 8-mers, said composition present in a dry state wherein the composition further contains at least one of: a polymerase enzyme; a supply of nucleotides for chain extension; a labeled nucleotide; a dye; a stabilizer and a buffer.